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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/656,309	09/06/2000	Walter Callen	DIVER1350-2	9418

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/21/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/656,309	CALLEN ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42 and 53-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42 and 53-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 19 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/4/2003 has been entered.

Applicants cancellation of claims 1-30, 43-52, amendment of claims 31, 53, 65 and 77 and the addition of new claims 89-97, Paper No. 22, 8/6/2003, is acknowledged. Claims 31-42 and 53-97 are at issue and are present for examination.

Applicants' arguments filed on 8/6/2003, Paper No. 22, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Applicant is reminded of the new procedure for the amendment of claims, as applicants state that prior to applicants amendment to the claims, "This listing of claims will replace all prior versions, and listing, of claims in the application". Applicants then state at the beginning of the "Remarks" section under the status of the claims, that "Claims 31 to 42 and 53 to 88 are pending (claims 1 to 30 and 43 to 52 have been canceled). It is pointed out to applicants that the newly submitted version of the claims

to replace all prior versions, and listing, of claims in the application, is missing claims 32-42, which as per applicants statements are still pending. Applicant is reminded of the proper procedure for the amendment of claims.

Claim Objections

Claims 31, 53, 65 and 77 are objected to because of the following informalities:

Claims 31, 53, 65, 77 each recite in their preamble "A method of generating a nucleic acid encoding a polypeptide having a polymerase activity..." while within the method steps of each claim they each recite "...to generate a variant nucleic acid that encodes a polypeptide having polymerase activity". It is suggested that applicants maintain consistency throughout the application, specifically with respect to the phrases "nucleic acid encoding a polypeptide" and "nucleic acid that encodes a polypeptide". The latter is suggested.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-42 and 53-97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Previously claims 31-88 were rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a selection step in which the generated variant is tested or screened such to determine which of the generated variants encode a polypeptide having polymerase activity. Applicants claimed methods would not generate a variant that encodes a polypeptide having polymerase activity without the above omitted step. In fact the majority of species of applicants claimed genus of methods would result in polypeptides which do not have polymerase activity. In response to this previous rejection applicants cancelled many of the above claims and amended those claims not cancelled.

Claims 31 (claims 32-42 and 89-97 dependent on), 53 (claims 54-64 dependent on), 65 (claims 66-76 and 89-97 dependent on), and 77 (claims 78-88 dependent on), are each indefinite in that they are confusing in the newly added recitation "and screening the polypeptide for a polymerase activity, thereby generating a polypeptide having a polymerase activity." It is acknowledged that this "screening step" was added to the claims as a means of overcoming the previous 112 2nd paragraph rejection, however, as the claims are drawn to a method of generating a nucleic acid encoding a polypeptide having a polymerase activity, this last step "thereby generating a polypeptide having a polymerase activity" is confusing. Is it not applicants intent to generate a **nucleic acid encoding** a polypeptide having a polymerase activity, or a polypeptide having a polymerase activity?

Claims 91 is indefinite in that it is directed to the methods of claim 31 or claim 65, wherein the polymerase activity comprises a 3'-5' exonuclease activity. The recitation "wherein the polymerase activity comprises a 3'-5' exonuclease activity" is confusing in that while it is understood that a polymerase polypeptide can have a 3'-5' exonuclease activity, it is unclear how a "polymerase activity" can comprise a 3'-5' exonuclease activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-76, 77-88 and 89-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to claims 31-42 , 65-76 and 77-88. Applicants have amended claims 31, 53, 65 and 77 and traverse this rejection as it applies to these new claims.

Applicants submit that the claimed invention is sufficiently described such that one of ordinary skill in the art would be able to recognize that Applicants were in possession of the claimed invention at the time of filing. Applicants cite the USPTO guidelines concerning compliance with written description, and submit that the genus of

nucleic acids used in the claimed methods is described by structure and function and that all nucleic acids of the claimed genus must have at least 70% or more sequence identity to a sequence set forth in SEQ ID NO: 1. In response to this argument it is noted that those claims drawn to methods which use nucleic acids having 70% sequence identity to SEQ ID NO: 1 have been withdrawn from this rejection (i.e. claims 31-42) however those claims which remain rejected are drawn to methods of use of a nucleic acid which merely comprises a fragment of at least 30 consecutive nucleotides having at least 70% identity to the sequence set forth in SEQ ID NO: 1. Thus those claims which remain rejected under this section of the statute are drawn to methods of use of a far broader genus of nucleic acid molecules then merely those which have 70% sequence identity to SEQ ID NO: 1 and encode a polypeptide with polymerase activity. Applicants have not adequately described such a genus of nucleic acid molecules and thus have not adequately described methods of use of this genus. Applicants have not described a representative number of species of this genus of nucleic acid molecules, nor have applicants recited sufficient structural features of the genus.

Thus those claims drawn to the claimed method of use of the genus of nucleic acid molecules which merely comprise a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO: 1 remain rejected.

Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full,

clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Newly added claims 89-97 are included in this rejection for the same reasons that claims 65 remains rejected as discussed above.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 31-42, 65-88 and 89-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating a nucleic acid that encodes a polypeptide having polymerase activity comprising: obtaining a nucleic acid comprising SEQ ID NO:1 and sequences complementary thereto and modifying, deleting or adding one or more nucleotides in said sequence, wherein said variant maintains polymerase activity, does not reasonably provide enablement for any method of generating a nucleic acid that encodes a polypeptide having polymerase activity: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence comprising a sequence having at least 70% identity to SEQ ID NO: 1 or a nucleic acid comprising a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO: 1 and encoding a polypeptide having polymerase activity or its complement and modifying, deleting or adding one or more nucleotides in said sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to claims 65-88. Applicants have amended claims 65 and 77 and traverse this rejection as it applies to these new claims. It is acknowledged that in addition to newly added claims 89-97, claims 31-42 have been added to this rejection because after further reconsideration applicants previous arguments are not found persuasive for reasons discussed below.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 31-42, 65-88 and 89-97 are so broad as to encompass any method of generating a nucleic acid that encodes a polypeptide having a polymerase activity comprising obtaining a nucleic acid comprising a sequence having a mere 70% identity to the sequence set forth in SEQ ID NO: 1 or a nucleic acid sequence comprising a fragment of at least 30 consecutive nucleotides of SEQ ID NO: 1 or a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO: 1 and encoding a polypeptide having polymerase activity or its complement and modifying, deleting or adding one or more nucleotides in

said sequence to generate a variant that encodes a polypeptide having polymerase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims, including all methods of generating variant polynucleotides which encode enzymes with polymerase activity wherein said variant polynucleotide is a variant of any polynucleotide comprising a sequence that has 70% identity to SEQ ID NO: 1 or a polynucleotide comprising a fragment of at least 30 nucleotides of SEQ ID NO: 1 or comprising a fragment of at least 30 nucleotides of a sequence that is at least 70% identical to SEQ ID NO: 1.

The claims rejected under this section of U.S.C. 112, first paragraph, place minimal structural and functional limits nucleic acids used in the claimed methods. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is gives no guidance beyond the structure of SEQ ID NO: 1 as to how one would obtain and/or modify the polynucleotide of SEQ ID NO: 1 such that the variant generated encoded a protein which had the desired polymerase activity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all methods of modifications of any nucleic acid sequence having a mere 70% sequence identity to SEQ ID NO: 1, or comprising a fragment having 30 consecutive nucleotides of SEQ ID NO: 1 or those nucleic acids comprising a fragment having 30 consecutive nucleotides having at least 70% sequence identity to SEQ ID NO: 1, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting function/activity; (B) the general tolerance of SEQ ID NO: 1 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of SEQ ID NO: 1 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to generate desired variant and the fact that the relationship between the sequence of a

peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of the claimed genus having the desired function.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any method of generating a nucleic acid encoding a polypeptide having a polymerase activity, comprising obtaining a nucleic acid having merely 70% sequence identity to SEQ ID NO: 1, or comprising a fragment of 30 consecutive nucleotides having 70% sequence identity to SEQ ID NO: 1, and modifying, deleting or adding one or more nucleotides in said sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants continue to traverse this rejection on the basis that methods for changing or varying nucleic acids sequences were well known in the art at the time of invention and that there is no requirement that every way of carrying out an invention be expressly described.

Applicants argument is not found persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding a polymerase) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As such, claims 31-42 have been included with those rejected claims. As stated previously, the specification does not establish: (A) regions of the protein structure which may be modified without effecting function/activity; (B) the general tolerance of SEQ ID NO: 1 or those sequences comprising 30 contiguous nucleotides having a mere 70% sequence identity to SEQ ID NO: 1, to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of SEQ ID NO: 1 or those sequences comprising 30 contiguous nucleotides having a mere 70% sequence identity to SEQ ID NO: 1 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicants declaration (Exhibit D) stating that it was considered routine by one skilled in the art at the time of the invention to screen for multiple substitutions or multiple modifications in a nucleic acid sequence for functional variations is acknowledged, however, as stated above while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e. encoding a polymerase) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation.

Applicants pointing out that claims directed to a genus of polypeptides as described and enabled by the specific physical characteristic of stringent hybridization and function have been issuing from the USPTO recently and for many years is noted, however, applicants are also reminded that the applications from which these cited claims issued are not the instant application and thus their relevance to those rejections made to the instant claims are questioned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
10/16/2003